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REVIEW ARTICLE

# Skeletal SPECT/CT: a review

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**Abstract** Skeletal scintigraphy is one of the most frequent in vivo procedures in the field of nuclear medicine. Visualizing bone metabolism, it exhibits a fairly high sensitivity to detect skeletal lesions, but has limitations in terms of specificity and spatial resolution, even when single-photon emission computed tomography (SPECT) is used. Combining SPECT with X-ray computed tomography helps overcome these limitations. This has, in particular, been shown when diagnosing bone involvement in malignant tumors. Emerging evidence indicates the benefit of hybrid imaging for bone scintigraphy during the workup of painful conditions affecting the back and the extremities. Methodological advances holding considerable promise for further improving its value are the quantitation of skeletal tracer uptake in absolute units, as well as multimodal image reconstruction techniques that have recently become available for use in clinical routine.

**Keywords** SPECT/CT · Bone scintigraphy · Skeleton

## Introduction

The quantification of bone metabolism was among the first applications of tracers in biology. The letter to *Nature* published in 1935 by George de Hevesy, which earned him the Nobel Prize in 1943, described the use of radioactive phosphorus to investigate bone metabolism in rats [1]. De Hevesy concluded from his results that "the formation of bones is a dynamic process", thus laying the foundation for many approaches to the study of bone metabolism that nuclear medicine developed over the following decades.

The $^{99m}$Tc-labeled polyphosphonates that are used today were introduced approximately 40 years ago [2]. Scintigraphic images acquired early after their intravenous injection provide information on perfusion and floridity of skeletal lesions (for a general review, see [3]). Scintigraphy performed several hours after tracer injection therefore allows insight into bone metabolism or, more specifically, osteoblastic activity, since the polyphosphonates are adsorbed on freshly built bone tissue [4, 5]. Initially, bone scintigrams were planar images, acquired either as spot views or as whole-body images. Due to the sensitivity of this examination to detect osseous lesions, skeletal scintigraphy has been widely used as a screening tool, e.g., for staging malignant disease. In the late 1980s, single-photon emission computed tomography (SPECT) became widely available, allowing three-dimensional visualization of the distribution of radioactivity within the human body. This technology considerably improved the diagnostic accuracy of bone scintigraphy by allowing better localization of areas exhibiting pathological tracer uptake (for a review, see [6]). Nevertheless, due to limitations in the spatial resolution of skeletal SPECT, which ranges from ca. 8 to 10 mm in the reconstructed images, the specificity of skeletal scintigraphy is still limited. This is true particularly when it is compared to radiological techniques such as X-ray computerized tomography (CT) or magnetic resonance imaging (MRI), the latter technique also allowing visualization of soft-tissue structures associated with bone, such as tendons, ligaments and cartilage, that elude bone scintigraphy for obvious methodological reasons.

Color figures online at http://link.springer.com/article/10.1007/s40336-014-0090-y.

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Approximately 12 years ago, the first hybrid system integrating a SPECT camera with a CT scanner into a single gantry became commercially available (for a review, see [7]). The CT component of this system utilized a low-dose, non-spiral CT scanner, whose images lacked diagnostic quality but allowed fairly precise localization of SPECT foci of abnormal tracer uptake, CT diagnosis of gross morphological abnormalities, and attenuation correction of the SPECT images as well. Since then, these technologies have considerably advanced, with current SPECT/CT systems offering a wide array of diagnostic quality, multislice spiral CT scanners (for review, see [8]).

This article reviews scientific evidence on the utility of SPECT/CT for bone scintigraphy following intravenous injection of Tc-99m-labeled polyphosphonates. As regards its value in imaging osteomyelitis with tracers concentrating in infectious and inflammatory lesions, the reader is referred to the review article specifically covering this topic, published in this issue of *Clinical and Translational Imaging* [9].

Using the terms SPECT/CT, SPECT-CT and skeletal, we conducted an electronic search of the PubMed database without language restrictions. The list of articles generated was augmented by retrieving further pertinent publications from the reference lists of the papers found in PubMed. Due to heterogeneities in study design, we did not perform meta-analyses or any evidence-based quality assessment of the available evidence.

## Technical considerations

The SPECT portion of a SPECT/CT examination is, in principle, no different from SPECT performed using a stand-alone system. For skeletal CT, the intravenous injection of contrast medium is not usually necessary. With the hybrid systems featuring a multislice spiral CT scanner, a CT examination of the skeleton of full diagnostic quality is possible, at least in principle. A literature survey shows, however, that even when such CT scanners are available, low-dose CT protocols with tube current–time products ranging from 15 to 60 mAs are generally used [10]. Furthermore, and contrary to the practice encountered in radiology, in a significant proportion of the studies so far published, the CT field of view is restricted to the region of the body harboring abnormalities of tracer uptake visible on the planar scintigraphic images. With this so-called SPECT-guided low-dose CT, as introduced by Römer et al. [11], the average radiation doses delivered to the patient are reduced between 2 and 3 mSv in most cases and thus correspond to doses incurred by patients having planar radiographs or non-diagnostic CT scans with SPECT/CT cameras not equipped with a spiral CT.

When SPECT/CT is used for staging, the results reported for the SPECT/non-diagnostic CT systems, as well as those obtained using SPECT-guided low-dose CT protocols, do not seem to be inferior to those obtained with the SPECT/diagnostic CT methodology (see below). Direct proof in support of this thesis is, however, lacking. In the case of staging, the major advantage of hybrid imaging resides in its potential to differentiate degenerative from neoplastic tracer-avid lesions in the axial skeleton (see below) where the bones involved are usually quite large and the anatomy less complex than in the peripheral skeleton. Furthermore, hot spots related to joint and spinal degeneration, as opposed to osseous metastases, typically project to the bony interfaces in question; thus, the foci localization capability provided by SPECT/non-diagnostic CT would, in principle, suffice for differential diagnosis. Therefore, the assumption of nearly equivalent performance of non-diagnostic and diagnostic CT protocols when using skeletal SPECT/CT for staging seems plausible.

This may, however, not necessarily be the case when SPECT/CT is performed for the workup of pain occurring in anatomically more complex regions of the body such as the wrists or the feet. Using SPECT/high-resolution flat-panel CT, Lohrmann et al. [12] have indeed demonstrated that diagnostic confidence scores and inter-observer agreement, as well as diagnostic accuracy, are all significantly higher with high-resolution CT images than with low-resolution ones, the latter being generated in their study by filtering the former.

The advantage of SPECT/CT, compared to the side-by-side evaluation of datasets acquired independently of each other, is the possibility of integrating the information from both modalities at pixel level. The average anatomical accuracy of alignment between the two sets of images is usually better than 2 mm in the lumbar spine and 5 mm in the neck and in organs affected by respiration [13, 14]. This error can be further reduced by applying additional image fusion software to the preregistered images. The greater SPECT/CT misalignment encountered in parts of the body subject to respiratory motion is due to the longer acquisition times of SPECT compared to spiral CT which generally captures these body regions in one phase of the respiratory cycle. Contrary to positron emission tomography (PET)/CT, respiratory gating protocols are not yet commercially available for SPECT/CT, rendering routine correction for these artifacts, at the time of writing, unfeasible.

On the basis of CT information, which is directly related to photon tissue absorption, the SPECT images of SPECT/CT can be attenuation corrected to yield a more realistic and homogeneous image of tracer distribution (for reviews, see [15, 16]). In this case, an important prerequisite is, however, that the alignment between CT and SPECT images is well below the SPECT pixel width; otherwise, attenuation artifacts may lead to false interpretation of the images [17].

For image interpretation, both image datasets are displayed simultaneously, with one overlaid on top of the other. As is also the case when interpreting stand-alone SPECT images, care should be taken to standardize SPECT windowing and color tables when assessing the significance of uptake in lesions. CT images should primarily be viewed using a window optimized for bone viewing centered on 500 Hounsfield units (HU) with a window width of 1,500 HU. In order not to miss extra-osseous pathology, CT scans should subsequently also be analyzed using windowing similarly optimized for lung and soft-tissue viewing. A SPECT/CT pattern-oriented approach to diagnosis has recently been published [18], providing some guidance on how to integrate the information from both modalities and arrive at a specific diagnosis.

## SPECT/CT for staging malignant bone disease

Skeletal lesions most frequently arise as a result of metastatic disease from primary tumors in other organs. Metastatic disease to the skeleton occurs in about 30 % of cancer patients, and identification of bone involvement is mandatory for correct staging and subsequent therapy. Skeletal metastases are frequently amenable to detection by bone scintigraphy with the $^{99m}$Tc-labeled polyphosphonates, e.g., $^{99m}$Tc-methylene diphosphonate. This imaging procedure affords visualization of the entire skeleton with an extremely high sensitivity, approaching 100 % for breast and prostate cancer (for reviews, see [6] and [19]). Purely lytic metastases such as those due to renal carcinoma or plasmocytoma may not increase bone metabolism and thus escape diagnosis by bone scintigraphy. This is also the case of sclerotic neoplastic osseous foci after treatment, e.g., with bisphosphonates, which are occasionally difficult to differentiate from bone islands.

The specificity of bone scintigraphy is rather low, as benign conditions, too, may be accompanied by an increase in bone metabolism. Pertinent examples are spinal degenerative conditions such as osteochondrosis and spondyloarthropathy, as well as osteoporotic fractures of the vertebral bodies. They pose a particular problem as they have a very high incidence in elderly subjects—an age group in which malignant disease is common. In addition, benign primary bone tumors such as enchondromas or fibrous dysplasia, as well as inflammatory diseases such as osteomyelitis, may be difficult to differentiate from metastases on the basis of radionuclide bone imaging alone. Its rather low specificity, therefore, often necessitates further investigation with, e.g., planar X-ray radiography, CT or MRI.

In the case of indeterminate bone lesions detected by bone scintigraphy for which a definite diagnosis cannot be reached, SPECT/CT offers the unique opportunity to directly correlate the scintigraphic findings with CT images to improve lesion classification (Fig. 1). Immediately after the introduction of the first hybrid SPECT/CT system in 2006, this advantage was investigated systematically in a trio of studies.

Horger et al. [20] studied 47 patients with 104 equivocal lesions on bone scintigraphy, taking histological confirmation or long-term follow-up as the reference gold standard. SPECT/CT allowed correct diagnosis in 85 % of the cases, particularly by improving characterization of the true nature of focal areas in the spine, ribcage, skull and pelvis. The term "SPECT-guided CT" refers to the adaptation of the CT field of view to foci of increased bone metabolism and was introduced by Römer et al. [11]. Using this method in 52 indeterminate lesions in 44 patients, 92 % of abnormal uptake foci visualized by SPECT/CT were correctly classified, with a pronounced benefit for lesions in the spinal column, ribs and pelvis. In addition to the improved diagnostic accuracy obtained by correlating functional with morphological images, Utsunomiya et al. [21] also reported a better diagnostic confidence for fused SPECT/CT image datasets than for side-by-side viewing of images from the two modalities.

Since these three initial reports, at least seven further publications have analyzed the potential of SPECT/CT to elucidate osseous hypermetabolic foci [22–29]. Table 1 gives a rough overview of the characteristics of each of these different studies and the results obtained. Despite various apparent weaknesses in the available evidence, linked to heterogeneities in study design, the results obtained are remarkably consistent: SPECT/CT enables a definitive diagnosis in between 71.0 and 95.3 % of lesions deemed equivocal on planar scintigraphy/SPECT (planar/SPECT) imaging [11, 23–25, 27]. SPECT/CT with bone-seeking radiopharmaceuticals is becoming a cost-effective, standard-of-reference imaging technique in the evaluation of patients with various types of cancer.

## Differential diagnosis of pain associated with the musculoskeletal system

Although MRI currently represents the standard of reference for benign orthopedic disease, bone scintigraphy is still frequently used for these indications due to its cost-effectiveness and the high sensitivity to osseous lesions and the complete view of the skeleton it provides. However,

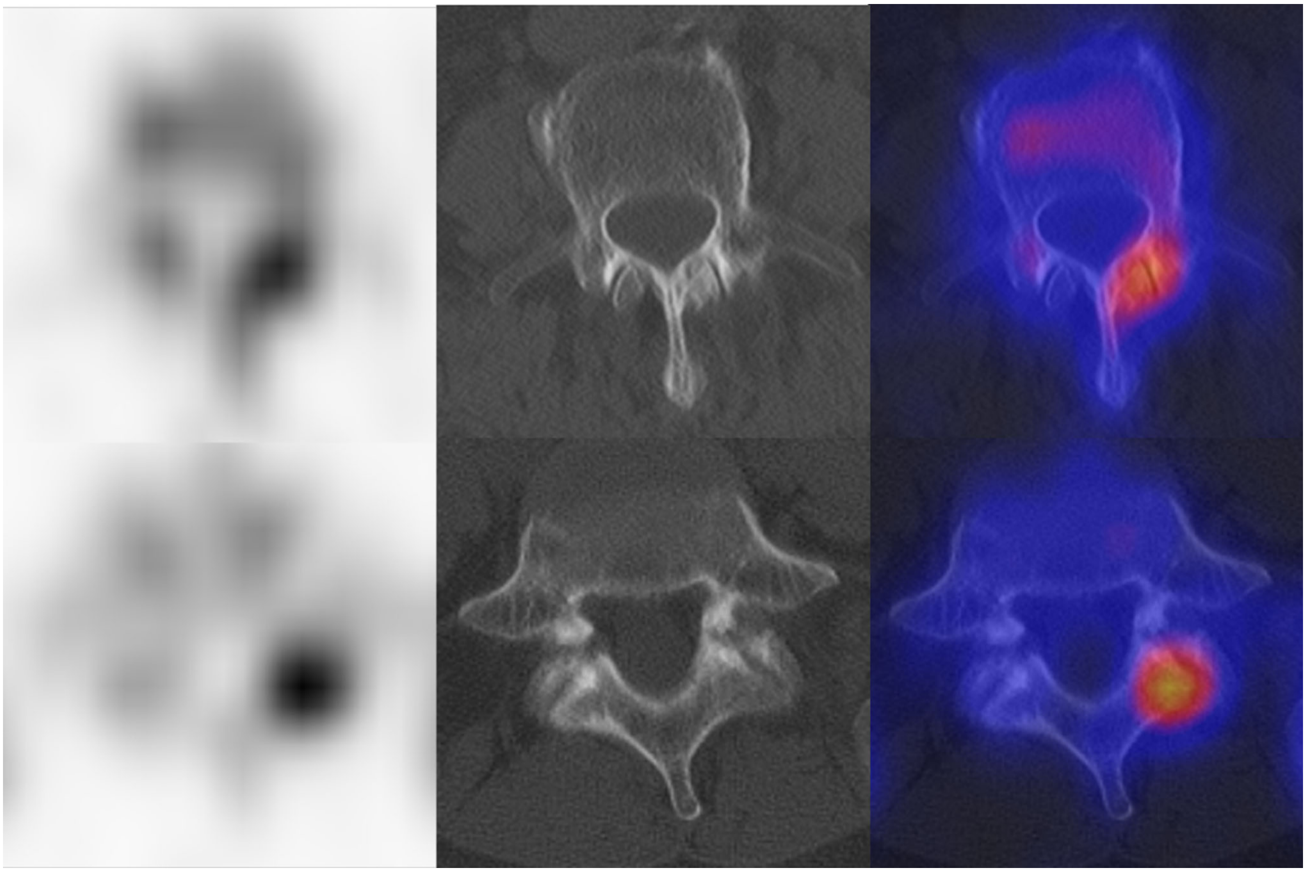

**Fig. 1** Transaxial SPECT, CT and SPECT/CT fusion images through a lumbar vertebral body from two patients with breast cancer (*upper* and *lower row*). The focus of abnormal tracer accumulation in the upper row of images is explained by arthritis of the facet joint, exhibiting joint space narrowing, subchondral sclerosis and osteophytes. In the lower row of images, maximal tracer uptake projects slightly behind the joint space to a region that is less dense than its contralateral counterpart. This constellation points to a small osteolysis in the posterior arch of that vertebral body (color figure online)

aside from its inability to visualize the soft-tissue structures of the joints, its major drawback is its low specificity.

SPECT/CT appears to overcome most of the diagnostic limitations of purely nuclear bone scintigraphy by allowing precise anatomical localization of bone turnover abnormalities. This advantage is also useful in non-oncological diseases (for recent reviews, see [30–34]).

One early retrospective study systematically analyzed the clinical benefit of SPECT/CT in benign orthopedic conditions of various origins pooled from all body regions. These authors investigated data from 89 consecutive non-oncological patients with inconclusive bone scans, for which further correlation with morphological imaging was required [35]. Rather than histological confirmation, consensus opinion between two nuclear medicine physicians and one musculoskeletal radiologist served as a gold standard. In 59 % of the subjects, multislice low-dose CT added to SPECT was critical for diagnosing the lesions as either fractures, osteochondral lesions, non-ossifying fibroma, enchondroma, fibrous dysplasia, herniation pits, spurs, posterior osteophytes, osteoid osteomas, bursitis, osteoarthritis, exostosis, spondylolysis, hemilumbalization or vertebral collapse. In another 30 % of the patients, SPECT/low-dose CT was used to optimize further patient imaging procedures. In the light of these findings, the authors concluded that SPECT/low-dose CT represented a clinically relevant component of the diagnostic process in patients with non-oncological orthopedic conditions referred for bone scintigraphy.

More specific evidence is continuously emerging in support of this conclusion. Below we first review findings regarding painful conditions affecting the axial skeleton and then provide a commentary on those concerning the appendicular skeleton.

*Axial skeleton* Bisphosphonates are increasingly used to treat lytic bone metastases as they reduce pain, pathological fractures, limited mobility, malignant hypercalcemia and spinal cord compression (for a review, see [36]). Osteonecrosis of the jaw is one of the complications associated with this therapy, particularly when it is given intravenously, and potentially affects up to 6.7 % of patients treated with these drugs. Besides conservative

**Table 1** Overview of studies reporting rates of SPECT/CT elucidation of hypermetabolic foci found on skeletal planar/SPECT images in cancer patients

| References | Study design | Independent gold standard?[a] | CT[b] | Number of lesions | % Elucidated by SPECT/CT |
|---|---|---|---|---|---|
| Horger et al. [20] | Prospective | Yes | Low-power X-ray tube | 104 | 85 |
| Römer et al. [11] | Retrospective | No | Low-dose spiral CT (40 mAs) | 52[c] | 92 |
| Helyar et al. [23] | Retrospective | No | Diagnostic spiral CT (100 mAs) | 50[c] | 92 |
| Zhao et al. [24] | Prospective | Yes | Diagnostic spiral CT(140 mA) | 37[c] | 86.5 |
| Ndlovu et al. [27] | Prospective | Yes | Low-power X-ray tube (2.5 mA) | 58[c] | 71.1 |
| Sharma et al. [25] | Retrospective | Yes | Diagnostic spiral CT (100 mAs) | 65[c] | 95.3 |
| Zhang et al. [29] | Retrospective | Yes | Diagnostic spiral CT (160 mA) | 90[c] | 94.4 |
| Sharma et al. [26] | Retrospective | No | Diagnostic spiral CT (100 mAs) | 36 (Skull only) | 100 |

[a] Gold standard was, in most studies, clinical and radiological follow-up, pathological diagnosis was available only in rare instances

[b] All studies listed in this column used dual-headed SPECT cameras in conjunction with the CT scanners

[c] Number of lesions reported as equivocal on planar/SPECT imaging

treatment such as antibiotics, operative resection of the necrotic core is usually performed. The diagnosis of this condition is usually based on typical symptoms and the detection of an unexposed extraction socket upon inspection. Imaging helps in differentiating this condition from neoplastic spread or radiation-induced osteonecrosis and in defining the extent of the osteonecrotic core. On bone scintigrams, increased tracer uptake in all three phases is usually seen. With planar and stand-alone SPECT imaging, a clear delineation of the necrotic tissue is not usually feasible, and SPECT/CT is thus an option to serve this purpose. In 2009, Dore et al. [37] assessed the value of this technology in diagnosing osteonecrosis of the jaw associated with intravenous bisphosphonate therapy in a group of 15 patients. They demonstrated that SPECT/CT allowed delineation of the osteonecrotic core, even in the presence of nearby hyperactivity due to viable bone. In their selected group of patients, MRI was unable to visualize bone loss, but proved helpful to detect soft-tissue involvement, suggesting the need for a multimodal approach to this disease including SPECT/CT.

Lower back pain has a very high incidence in western populations and a vast gamut of differential diagnoses (for a review, see [38]). Disk herniation is not amenable to bone scintigraphy and can only be diagnosed by MRI. Active degenerative disease of the axial skeleton, however, being accompanied by an increase in polyphosphonate uptake, is amenable to bone scintigraphy (Fig. 2). This applies to osteochondrosis radiologically characterized by disk space narrowing, subchondral sclerosis of the vertebral bodies, osteophytes, and radiological signs of disk degeneration such as the occurrence of gas in the disk—the so-called vacuum phenomenon. More relevant to clinical management is the detection of active osteoarthritis at facet joints, as this diagnosis and localization helps in directing topical therapies such as a medial branch block or intra-articular instillation of corticosteroids.

Active facet joint disease can be diagnosed by SPECT/CT: Matar et al. [39] reported a frequency of 65 % for metabolically active facet joint disease in 72 patients referred for SPECT/CT for workup of chronic neck or back pain. In their retrospective study, SPECT/CT identified potential pain generators in 92 % of the study population. Makki et al. [40] reported that 91.1 % of 486 patients consecutively studied by SPECT/CT for spinal pain over 7.5 years had at least one abnormality visible on SPECT/CT potentially causing the symptoms. In their cohort, they found a prevalence of 42.8 % of subjects with increased uptake in at least one zygapophyseal joint. In a further large retrospective study, Lehmann and coworkers analyzed data from 212 patients referred to their department for spinal SPECT/CT over a period of roughly 4 years [41]. 191 of these subjects had been examined for workup of back pain, with suspicion of abnormal facet joint activity being the most frequent indication (37 % of the total). In 50 % of the whole group, pathological uptake was described in at least one facet joint. Most noteworthy, 40 % of the whole group had undergone SPECT/CT after prior MRI examinations, and 35 % of the subjects referred for differential diagnosis of pain had had prior percutaneous interventions with incomplete response. As recorded on the treating physicians' clinical notes, SPECT/CT findings led to a change in clinical management in 79 % of patients, a result that impressively documents the level of acceptance and the utility of hybrid SPECT/CT imaging.

The evidence presented above suggests that skeletal SPECT/CT might have the potential to guide percutaneous therapy of facet joint arthritis. Additional data on the use of stand-alone SPECT also point in this direction [42–44]. In a further publication, however, Lehmann et al. [45], in a

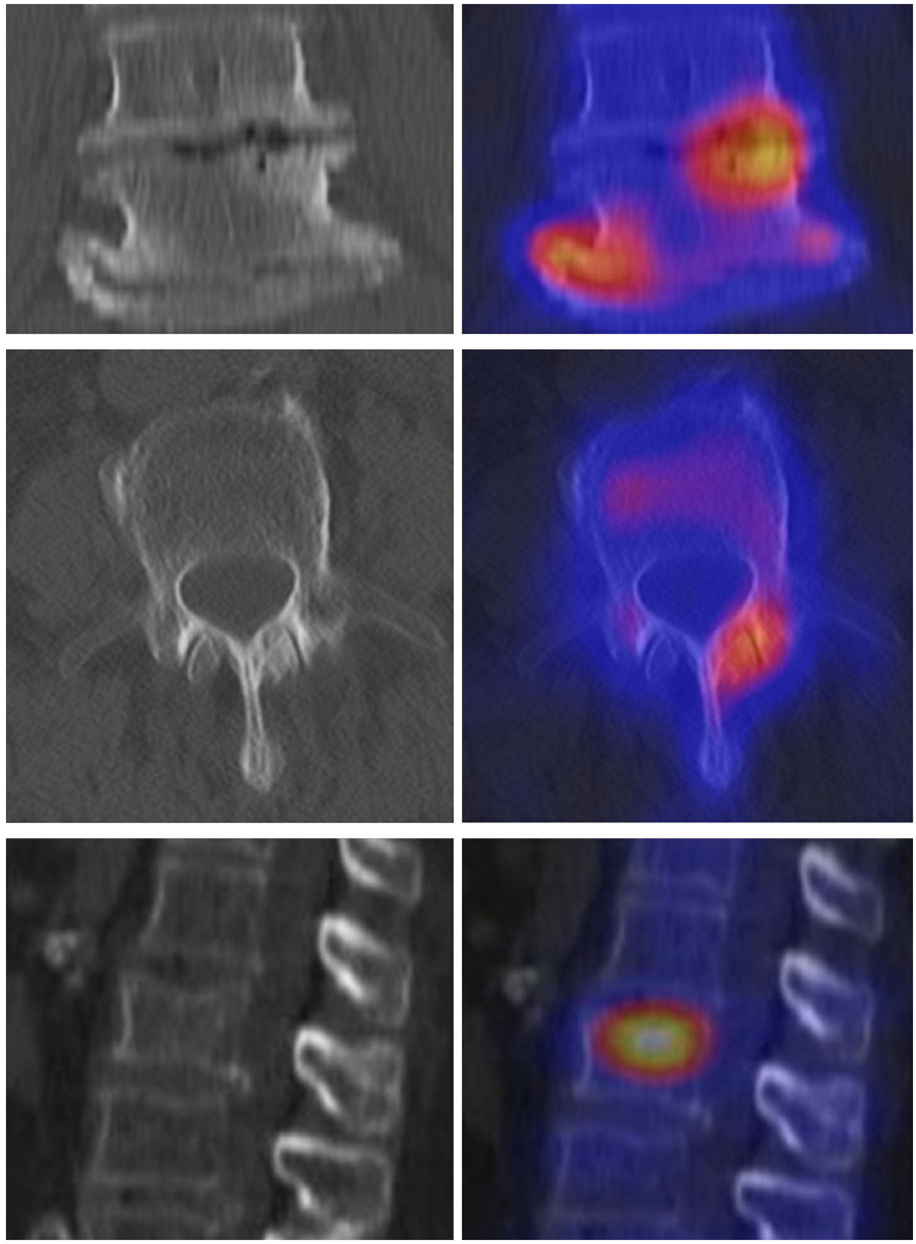

**Fig. 2** Common causes of back pain as seen on CT (*left column*) and SPECT/CT fusion (*right column*): *upper row* Osteochondrosis with gas in the intervertebral disk as a sign of its degeneration (vacuum phenomenon), subchondral sclerosis, and metabolically active osteophytes. *Middle row* facet arthritis with subchondral sclerosis and osteophytes. *Lower row* impending compression fracture of a lumbar vertebral body with increased tracer uptake in the end plate and accompanying end plate impression (color figure online)

group of 74 patients, analyzed the relationship between the localization of abnormal tracer uptake in the facet joint and the joint percutaneously treated. In 70 % of these subjects, site of treatment and SPECT/CT abnormality did not coincide. Furthermore, 46 % of the subjects had a right versus left discrepancy. This shows that the relationship between the scintigraphic abnormality and the occurrence of back pain is not as straightforward as initially expected. The type of treatment is also a variable that should receive consideration in this context: in a prospective double-blinded outcome study, Ackerman and Ahmad showed that SPECT/CT performed better in predicting pain relief after intra-articular injections of cortisone than after medial branch blocks [46]. Clearly, more evidence from further prospective—ideally, double-blinded—investigations with pain relief as an outcome variable would be necessary to establish the value of SPECT/CT for planning local therapies of painful facet arthritis.

Another frequent cause of back pain, particularly in the elderly, is osteoporotic compression fracture of vertebral bodies. Within the first year of occurrence, this condition is metabolically active and can thus be visualized by bone scintigraphy. SPECT/CT may help in localization and also in differentiating this condition from metabolically active osteochondrosis. Vertebral osteoporotic fractures may be treated by percutaneous vertebroplasty. In a recently published prospective study of 33 consecutive patients with this condition, positive SPECT/CT images predicted, in 91 % of these subjects, clinical improvement induced by this minimally invasive procedure [47]. Furthermore, it identified alternative causes of pain in the subgroup of nine patients in whom the therapy in question had not been performed. It can be surmised, on the basis of anecdotal evidence, that SPECT/CT might also be helpful in acute spinal traumas and, in particular, in diagnosing stress fractures in bilateral pedicles of the spine, as can occur in athletes [30].

Spinal fusion surgery is performed in patients with severe chronic back pain when segmental instability is believed to be the cause of the symptoms (for review, see [48, 49]). The rationale for this is that pain relief will be achieved once the fusion restricts motion in the painful segments. An estimated ten to twenty percent of patients develop lumbar pain after lumbar fusion surgery. This may be related to loosening of the metallic implants or failure of a stably implanted graft to immobilize the fused segments. A further differential diagnosis is degenerative disease involving the spinal segments above or below the instrumented region. Differentiation between these conditions has therapeutic consequences: in the first case, a complementary ventral spondylodesis must be considered, in the second an amplification of the instrumentation in cranial or caudal direction. Near to metallic implants, CT quality is considerably degraded by streak artifacts and that of MRI by susceptibility phenomena, thus reducing the accuracy of these two modalities in differentiating between the above-described causes of pain after spondylodesis. Bone scintigraphy, which is either not affected by these artifacts or affected only indirectly via attenuation correction, might thus be of particular value for this purpose [50].

Sumer and coworkers compared skeletal SPECT/CT to planar/SPECT imaging in 37 patients suffering from back pain after lumbar fusion surgery [51]. SPECT/CT led to a change in diagnostic category in approximately half of the patients. The superiority of SPECT/CT over planar/SPECT was, however, not due to an increase in the sensitivity of SPECT/CT in detecting pathological foci of uptake compared to standard scintigraphic imaging. Rather, as when staging malignant disease, SPECT/CT improved the specificity of nuclear medical imaging via two avenues: (1) through its ability to localize pathological foci of uptake more precisely, and (2) through its capacity to characterize the CT morphology of the lesions underlying the increase in bone metabolism depicted by scintigraphy. These data suggest that planar/SPECT misses the correct diagnosis in roughly half the patients studied. It follows that they also indicate that, for similar patient cohorts, planar scintigraphy should be complemented by a SPECT/CT examination.

The publication by Sumer et al. lacks a gold standard which, in such cases, could take the form of an intraoperative examination of the stability of the implant in the course of a reoperation. Damgaard et al. [52] performed such a study and indeed showed that this evaluation confirmed the SPECT/CT diagnosis of metal loosening in their sample of nine patients suffering from lower back pain after lumbar instrumentation. Similar data have been published by Rager et al. [53]: in their case series of ten patients, all screws deemed loosened on reoperation had corresponding increased tracer uptake on SPECT/CT. In six cases, metabolic activation was found in facet joints that had no CT abnormality, and in three of five subjects SPECT/CT did not confirm the CT diagnosis of nonunion through or around cages. SPECT/CT thus holds considerable promise in this field and further prospective studies further underscoring its value would be of utmost interest.

*Appendicular skeleton* A wide array of conditions may lead to pain of the extremities. Imaging workup usually starts with planar radiographs, followed by CT or MRI, depending on the differential diagnoses under consideration by the treating physician. Bone scintigraphy is another option, but in this setting it, too, suffers from the aforementioned low specificity. Therefore, SPECT/CT has received considerable attention for such indications, as highlighted by several pertinent review articles [32, 33].

In a retrospective study, Linke et al. [54] reported 71 non-oncological patients with pain in the extremities who had undergone a conventional three-phase bone scan and SPECT/CT of either the arms ($n = 20$) or legs ($n = 51$). Four patients exhibited no abnormal bone metabolism or CT abnormality in the extremities. Of the 34 lesions classified as osteoarthritis on the planar/SPECT images, seven were reclassified as fracture and one as benign tumor by SPECT/CT; of the 15 lesions classified as osteomyelitis, four were diagnosed as osteoarthritis, four as fracture, and one as inflammation of the soft tissue only. Two of eight patients in whom a fracture had been diagnosed by the conventional approach were reclassified as osteomyelitis and two as osteoarthritis. In one of the ten patients diagnosed with a tumor-like lesion, the diagnosis was changed to trauma and in another to osteoarthritis on the basis of SPECT/CT findings. Overall, SPECT/CT led to revision of the diagnostic category in 23/71 patients (32 %; $\chi^2 = 10.82$, $p < 0.01$).

A multitude of further publications has addressed a range of more specific issues, such as SPECT/CT imaging of the feet and hands. SPECT/CT has been found to show good diagnostic accuracy in patients with obscure pain of the wrist or hand, being able to differentiate between osteoarthritic lesions, occult fractures and osteonecrosis [55–58]. A particularly elegant approach is that of combining SPECT/CT with arthrography, the latter yielding information on the intactness of articular cartilage and

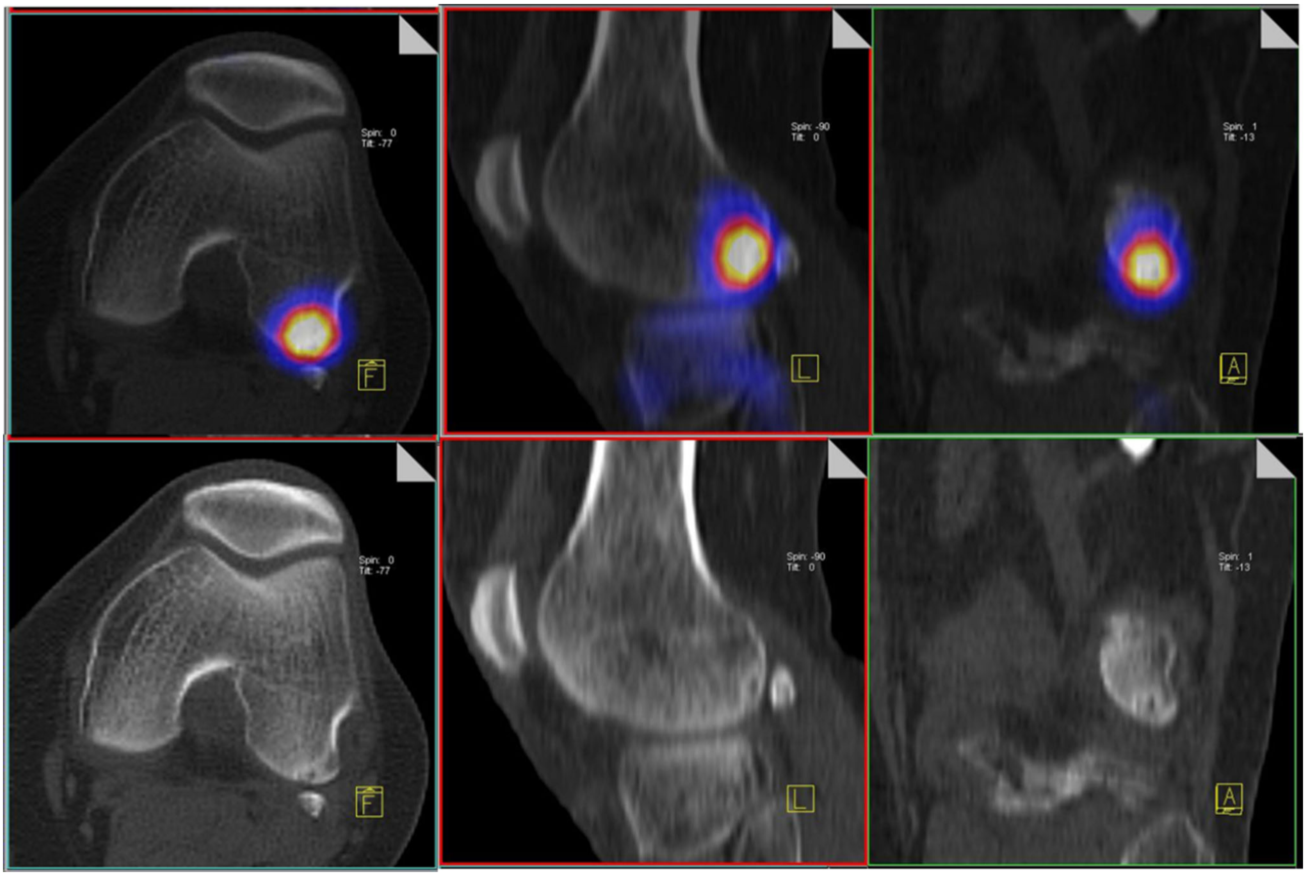

**Fig. 3** Metabolically active osteoarthritis between the femur and a small accessory ossicle, a fabella (CT in the three spatial orientations in the *upper row*, registered SPECT/CT fusion images in the *lower row*) (color figure online)

other soft-tissue structures such as the scapholunate and lunotriquetral ligaments [59].

Pain in the foot may be due to a plethora of different conditions, including osteoarthritis caused by accessory sesamoid bones, tarsal coalition and osteochondrosis dissecans. In addition, impingement syndromes, inflammation, trauma and soft-tissue pathologies may also give rise to complaints in the distal extremities. Pagenstert et al. [60] demonstrated an excellent inter-observer reliability of SPECT/CT in localizing osteoarthritic changes in the foot. Studying 50 patients with SPECT/CT of the foot in retrospect, Singh et al. [61] reported a change in the treatment plan in 78 % of subjects and a resulting accuracy of 94 %. The patients studied by these authors had, however, not previously received an MRI. In a prospective study, 27/30 (90 %) patients treated by infiltration with local anesthetics of the structures most active on SPECT/CT reported significant pain reduction [62]. Based on the available evidence and their own clinical experience, Mohan et al. proposed a diagnostic algorithm for the imaging of patients with chronic foot pain, recommending SPECT/CT as the first tomographic imaging procedure in patients with previous surgery or metal implants and as the second tomographic examination in cases with an inconclusive MRI [32].

Several review articles suggest the usefulness of SPECT/CT also for the workup of patients with pain in the shoulders and the hips [32, 33]. Original articles presenting conclusive evidence proving this plausible assumption are, however, still scarce. This also applies to the diagnostic role of SPECT/CT in painful hip implants.

Osteoarthritis of the knee has received more attention in the recent literature. Figure 3 presents a pertinent example. In a series of carefully conducted studies, Hirschmann et al. and Rasch et al. [63, 64] established that intensity of tracer uptake as visualized by SPECT/CT reflects the specific loading patterns of the knee with regard to its alignment and that abnormal increases in tracer uptake are reversible on tibial osteotomy correcting for varus misalignment [65, 66]. Furthermore, they proposed a standardized, semi-automatic approach for the evaluation of tracer uptake in the knee in relation to component position following arthroplasty [67]. Using this method, they demonstrated that SPECT/CT imaging had therapeutic impact in 19/23 of

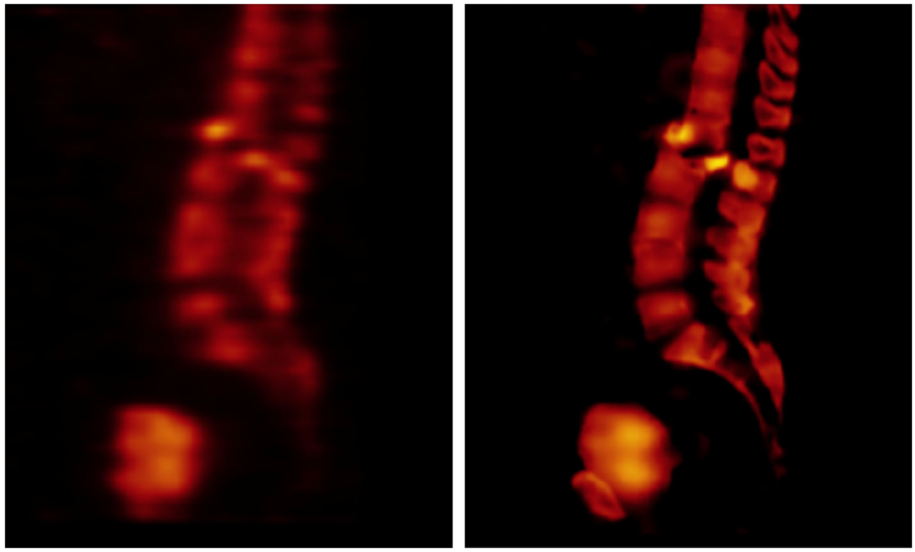

**Fig. 4** Sagittal SPECT images of the spine in a patient with a compression fracture of lumbar body 1. The multimodally reconstructed dataset (*right*) provides superior delineation of the osseous structures compared to the dataset reconstructed using a conventional ordered subsets maximum-likelihood algorithm (color figure online)

the knees studied [68]. In a review article, Hirschmann et al. [69] proposed a central role for SPECT/CT for evaluating painful knee arthroplasty and recommended it as a second imaging procedure after planar radiography.

## Methodological perspectives

For some years now, another nuclear medical technique for studying bone metabolism, i.e., PET with F-18-fluoride, has been a focus of increasing attention (for reviews, see [70, 71]). Some studies comparing its diagnostic performance in staging malignant disease with that of conventional nuclear medical bone imaging have demonstrated its superiority over planar bone scans and—albeit to a lesser degree—also over SPECT [72–75]. Evidence comparing F-18-fluoride PET/CT to skeletal SPECT/CT is still scanty [76], but nevertheless also indicates a slightly higher accuracy of PET/CT compared to hybrid SPECT/CT imaging for diagnosing osseous spread of malignancy. These results seem plausible in view of the superior imaging qualities of PET compared to SPECT, including its higher spatial resolution and its ability to measure tissue radioactivity concentration in vivo. Nevertheless, some technological progress in the field of SPECT/CT might help fill the gap between these two technologies as detailed below:

Very recent advances in skeletal SPECT/CT provide the possibility of measuring the uptake of the Tc-99m-labeled polyphosphonates in absolute units, e.g., in kBq/ml, as well as the possibility of performing multimodal image reconstruction which dramatically improves SPECT image quality.

Quantitative SPECT (QSPECT) was first introduced into nuclear medicine in the 1990s. In 1995, Rosenthal et al. [77] predicted that estimates of absolute SPECT tracer concentration would enter the clinical arena in the near future. However, to date, their prediction has not come to fruition, as only a few approaches based on QSPECT have been established in clinical practice (for reviews, see [15, 16]).

One of the first QSPECT protocols validated in humans was reported by Willowson et al. [78], who quantified the concentration of Tc-99m in the cardiac cavity in patients studied by radionuclide ventriculography. Other work by our research group proposed a QSPECT protocol for quantifying the tissue concentration of Tc-99m [79]. Our methodology, as well as that of Willowson et al., involves the use of co-registered data from X-ray CT to correct for attenuation and a window subtraction approach (dual-energy window) to correct for scattered counts. In each of these two studies, a gold standard was provided via an independent measurement of a patient's blood or urine in an activimeter.

Building on the methodological setup developed by Zeintl et al. [79], we measured the activity concentration of Tc-99m-diphosphono-propanedicarboxylic acid in healthy spongious bone tissue, without focal SPECT and CT abnormalities, in 50 women referred for bone scintigraphy [80]. The concentration was found to be $48.15 \pm 13.66$ kBq/ml, translating into an average standardized uptake value (SUV) of $5.91 \pm 1.54$. These values are in the same range as those reported for F-18-NaF imaged with PET [81]. Furthermore, in this group of subjects, SUV determined in the vertebral bodies correlated significantly with the CT density of these bodies measured in HU ($r = 0.678$; $p < 0.0001$).

QSPECT of the bone might be of interest for modeling bone metabolism in osteoporosis and also for longitudinal monitoring of treatment response, e.g., in bone metastases.

The integration of QSPECT into commercially available SPECT/CT systems will surely encourage research into its clinical value over the coming years.

The addition of the CT component to stand-alone SPECT systems aids both image reconstruction and lesion localization. Today, SPECT images are typically reconstructed using iterative techniques which benefit from additional CT information via attenuation correction. Further integration of CT information has been achieved in a novel reconstruction algorithm from Siemens Molecular Imaging [82]. This method—known as xSPECT Bone—uses the higher resolution CT data to enhance reconstructed nuclear resolution at tissue boundaries. xSPECT Bone produces images of tracer distribution with considerably higher quality than conventional iterative reconstruction techniques do (Fig. 4). Preliminary evidence shows that the improvement in SPECT image quality translates into higher confidence of diagnosis when staging malignant disease. The potential to more precisely localize increases in tracer uptake within complex structures such as joints leads to the assumption that orthopedic imaging, too, will benefit greatly from this option.

## Conclusions

Skeletal scintigraphy is one of the most frequent in vivo procedures in the field of nuclear medicine. Visualizing bone metabolism, it exhibits a fairly high sensitivity to detect skeletal lesions, but has limitations in terms of specificity and spatial resolution, even when SPECT is used. Combining SPECT with X-ray CT helps overcome these limitations. This has, in particular, been shown when diagnosing bone involvement in malignant tumors. Emerging evidence indicates the benefit of hybrid imaging for bone scintigraphy during the workup of painful conditions affecting the back and the extremities. Methodological advances holding considerable promise for further improving its value are the quantitation of skeletal tracer uptake in absolute units, as well as multimodal image reconstruction techniques that have recently become available for use in clinical routine.

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**Conflict of interest** Torsten Kuwert has an ongoing research collaboration with Siemens Molecular Imaging in the field of SPECT/CT. He gives occasional lectures on behalf of Siemens Molecular Imaging pertaining to SPECT/CT research.

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